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13. ABSTRACT *(Maximum 200 words)*

Oligomers of chlorotrifluoroethylene (POLYCTFE) have been found to possess excellent properties as lubricants and hydraulic fluids. The 3.1 oil, consisting primarily of oligomers of 3 and 4 units, is a candidate base stock for nonflammable hydraulic fluids for advanced aircraft. Unfortunately, ultrastructural studies of the livers from rats exposed to vapors of POLYCTFE for 90-days revealed an increase in the number of peroxisomes, dose-dependent mitochondrial swelling and a dose-dependent increase in smooth endoplasmic reticulum. In order to determine the relevance of the effect of POLYCTFE on rat livers to human livers, four male rhesus monkeys weighing 8 to 10 kg were dosed by gavage daily for 15 days with 0.725 g/kg POLYCTFE. Wedge biopsies of liver obtained from each animal were collected and prepared for transmission electron microscopic examination. Repeated exposure of primates to POLYCTFE for 15-days resulted in only minor changes in the hepatocytes. There was no evidence of peroxisomal proliferation in exposed primate livers. Oligomers of CTFE did not produce the same effect in primate livers as in rat livers. The toxicity of POLYCTFE in rats may not be an appropriate indicator of potential human hazard.

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Proceedings of the XIIth International Congress for Electron Microscopy

ULTRASTRUCTURAL STUDY OF THE EFFECT OF POLYCTFE ON PRIMATE LIVER

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Polychlorotrifluoroethylene (POLYCTFE) existing as oligomers of 3 and 4 units, is a candidate base stock for a nonflammable hydraulic fluid for advanced aircraft. POLYCTFE caused significant changes in the livers of rats after repeated inhalation exposure.[1] Ultrastructural studies of the livers from rats exposed to vapors of POLYCTFE oligomers for 90-days revealed an increase in the number of peroxisomes, dose-dependent mitochondrial swelling and a dose-dependent increase in smooth endoplasmic reticulum.[2] The objective of this study was to ultrastructurally examine hepatocytes from the livers of primates exposed to POLYCTFE and compare the exposed primate hepatocytes to those from rat livers, in order to determine the relevance of the effect of POLYCTFE on rat livers to human livers.

Male rhesus monkeys weighing 8 to 10 kg were dosed by gavage daily for 15 days with 0.725 g/kg POLYCTFE. Four animals received POLYCTFE and 3 received a comparable amount of water. A laparotomy was performed on each animal at the end of the dosing period in order to obtain a wedge biopsy for analysis. A 1mm slice of the liver biopsy from each animal was collected for transmission electron microscopic examination. The liver slices were fixed in 2% glutaraldehyde in 0.1M cacodylate buffer at pH 7.4 and minced into 1 cubic mm pieces. The minced tissue was post-fixed with 2% osmium and was processed into EPOX 812 plastic capsules. One micron thick sections were cut in order to identify centrolobular zones. Thin sections were cut from the centrolobular and intermediate zones of liver lobules. Thin sections stained with uranyl acetate and lead citrate, were examined with a JEOL 100B electron microscope at 60 kV. For each animal 20-30 photographs were taken of 3 or more hepatocytes that were representative of the liver for that animal. The number of peroxisomes were counted per 30,000 magnification visual field using an 8 by 10 inch photograph. An average of 9 photographs were counted per each animal. Statistical analysis of peroxisome counts was conducted using the Student's T-Test at the $p<0.05$ level of significance.

Repeated exposure of primates to POLYCTFE for 15-days resulted in only minor cnanges in the hepatocytes with no evidence of peroxisomal proliferation (FIG. 1,2). The mean number of peroxisomes for control primate liver was 2.5 ± 0.33 ($\pm$ S.E.M.) compared to 3.3 ± 0.42 for exposed animals. The difference between the control and exposed values for peroxisomal counts were not statistically significant. Mild to moderate mitochondrial swelling was seen in both control (FIG. 3) and exposed animals (FIG. 4). A decrease in glycogen was seen in primates exposed to POLYCTFE (FIG. 2 or 4). POLYCTFE did not produce the same effect in primate livers as in rat livers.[2] Mitochondrial swelling seen in both control and exposed animals was probably a result of ischemia due to the method of obtaining the biopsy.[3] An observed decrease in food consumption by all animals could explain the decreased amount of glycogen in exposed animals. POLYCTFE did not produce the same effect in primate livers as seen in rat livers.

1. E.R. Kinkead et al., The Toxicologist 9(1989)144.
2. D.R. Mattie et al., Proc. Ann. EMSA Meeting 46(1988)330.
3. Dougherty, C., Personal Communication, 1989.

FIG. 1.--Hepatocyte from control primate liver cell showing normal number of peroxisomes (P). Bar = 1 um.
FIG. 2.--Hepatocyte from primate liver exposed to CTFE for 15-days showing normal number of peroxisomes (P). Bar = 1 um.
FIG. 3.--Control primate hepatocytes with glycogen (G) and swollen mitochondria (M). Bar = 1 um.
FIG. 4.--Primate hepatocyte from liver exposed to CTFE for 15-days with swollen mitochondria (M) and showing a decreased amount of glycogen (G). Bar = 1 um.